

### REMARKS

This Reply is being filed in response to the Office Action mailed from the U.S. Patent and Trademark Office on August 18, 2004, in which claims 1-53 were rejected under 35 U.S.C. §103(a). With this Reply, Applicants respectfully contend that the Office Action has not established a prima facie case of obviousness. As such, Applicants respectfully request withdrawal of the rejections under §103(a) and reconsideration and allowance of pending claims 1-53.

The Office Action rejected claims 1-53 under 35 U.S.C. §103(a) as being unpatentable over Benco et al. (*Journal of Photochemistry and Photobiology A*, 2002) ("the Benco reference") in view of U.S. Patent No. 4,659,815 to Pacey ("the Pacey reference") and U.S. Patent No. 6,417,005 to Barnard or PCT Publication No. WO 97/39337 to Barnard ("the Barnard reference").

Three criteria must be satisfied before a prima facie case of obviousness is established:

**...First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all of the claim limitations.**

The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in the applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed.Cir. 1991). (M.P.E.P. §2143)(Emphasis added).

The Applicants contend that these requirements have not been satisfied.

The Office Action cites and combines three references to reject the Applicants' claimed compound--**the claimed compound being a calixarene wherein the calixarene has been modified to selectively bind lithium ions when the compound is in the presence of lithium, potassium and sodium ions.** In summary of the cited references, the Benco reference, the primary reference, discloses a compound used to selectively detect potassium ions in the presence of lithium and/or sodium ions. As such, an advantage of the compound disclosed in the

Benco reference is that it DOES NOT detect lithium ions. Second, the Pacey reference teaches a compound that does detect lithium; however, the compound of the Pacey reference is NOT similar to the claimed compound of the current application. More specifically, the Pacey compound is NOT a calixarene but rather a crown ether. Finally, the Barnard reference discloses a compound that does not appear to **selectively bind** ions such as sodium, lithium and potassium (i.e., the Barnard reference is more directed towards a method of binding a compound to a sensor for use in a biological fluid).

The Applicants respectfully disagree that there is motivation to combine these references. Further, even if cited references are combined they do not disclose each of the claim limitations. As stated above, the Benco reference discloses a compound which detects potassium in a mixture of potassium, sodium and lithium--an advantage of the compound of the Benco reference is that it does NOT bind to lithium. The Office Action states:

...On page 37 there is a discussion of **selectivity**. The first sentence of this section teaches that the eventual intention is to use molecules similar to II as a sensor. The next sentence teaches that given the structural similarities between II and 1,3 alternate calix[4]arenes, it is reasonable to expect similar binding properties. **The next sentence teaches that they expect metal complexation in II to be governed by electrostatic interactions (primarily cation- $\pi$  interactions). That sentence also teaches that the selectivity is primarily controlled by a size fit effect and steric effects from the propyl substituents appended to the two rotated aryl rings of the calix[4]arene.** Benco does not teach an azacrown calix[4]arene sized to capture lithium or structures related to sensor formation. (August 18, 2004 Office Action; Pages 2-3)(Emphasis added).

The Office Action appears to be stating that since the Benco reference has stated that calixarenes of this general structure tend to attract potassium, lithium and/or sodium ions it would be obvious to one skilled in the art to know how to modify the structure to bind only to potassium or to bind only to sodium or to bind only to lithium ions. To the contrary, the highlighted passage above indicates the problem that the Benco reference is trying to overcome; i.e., **how can we modify a calixarene to bind only to potassium?** The Benco reference overcame this problem by disclosing the compounds shown on page 34, column 2 (the Benco reference served as the basis for U.S. Patent No. 6,660,526 B2). As such, the Benco reference is deficient because it does not disclose how one skilled in the art would modify the compound so as to bind lithium and ignore

potassium ions. Further, since the object of the Benco reference is to not bind to lithium ions, the Applicants do not believe there would be motivation to seek such a modification. As such, there is no support in the Benco reference regarding how to modify the structure of the Benco reference to bind to lithium ions and not bind to potassium ions--such support would be contrary to the purpose of the Benco reference.

The Office Action cited the Pacey reference as a cure for the deficiency of the Benco reference (the deficiency being 'how would one modify the calixarene of the Benco reference so that the compound would selectively bind to lithium?'). The Office Action stated:

In the patent Pacey teaches chromogenic aza-12-crown-4 ethers used for the spectrophotometric determination of lithium ion in aqueous solutions. The compounds are particularly useful for the analysis of lithium in the presence of  $\text{Na}^+$ , a situation common in biological and geological systems. The compounds [e.g., 1-(2-oxy-5-nitrobenzyl)-1-hydro-1-aza-4,7,10-trioxacyclododecane] are **similar in structure to compound I of Benco except they have a smaller crown and a colorimetric group appended to the crown**. Column 1, lines 30-43 teach that selective reagents permitting the isolation of a particular ion from a complex matrix or mixture of ions are of interest to those in the chemical or bio-chemical analytical fields. When the matrix in question includes two or more cations of the Group I metals, it is often difficult to selectively isolate one of the Group I cations from the mixture without interference from other cations in the system. With respect to biological systems, such as blood serum, which contains a relatively large amount of sodium ion, a reagent having the ability to selectively (and quantitatively) extract lithium ion in the presence of sodium ion is of interest for bio-chemical assays. Some examples of prior art molecules are taught with drawbacks being explained. Column 3, lines 11-19 and example 9 teach the selectivity of the molecules of the invention when lithium is complexed in the presence of a large excess of sodium. Example 7 shows the ability of the reagents to complex lithium in the presence of a potassium hydroxide buffer and example 11 shows the ability to measure lithium in blood and urine samples. These results shown in table 2 show excellent correlation with the known amount of lithium present. (August 18, 2004 Office Action, Page 3)(Emphasis added).

The Pacey patent does NOT teach how to modify the compound of the Benco reference so that the Benco reference discloses the compound of the present invention. In the Office Action's discussion of the Pacey patent, the Office Action states that the Pacey compound are "**similar in structure to compound I of Benco except they have a smaller crown and a colorimetric**

**group appended to the crown."** However, the current application only includes claims directed towards calixarenes with an aza crown (more analogous to compound II of the Benco reference). While the compounds disclosed in the Pacey reference may be similar in structure to compound I of the Benco reference (a crown ether), they are NOT similar in structure to the compound claimed in the current application. Clearly, there is no mention or motivation on how to modify compound II of the Benco reference so as to produce the compound of the current application--a compound which selectively binds to lithium.

Further, the M.P.E.P. states:

If proposed modification would **render the prior art invention being modified** [the Benco reference] **unsatisfactory for its intended purpose** [detecting potassium ions without detecting lithium ions], **then there is no suggestion or motivation to make the proposed modification**. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984). (M.P.E.P. §2143.01)(Emphasis added).

And:

If the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, **then the teachings of the references are not sufficient to render the claims *prima facie* obvious**. *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959). (M.P.E.P. §2143.01)(Emphasis added).

In this case, the primary reference is the Benco reference. The Benco reference discloses a compound which **selectively binds to potassium** in a mixture of sodium, potassium, and lithium ions. FIG. 3 on page 38 of the Benco reference shows:

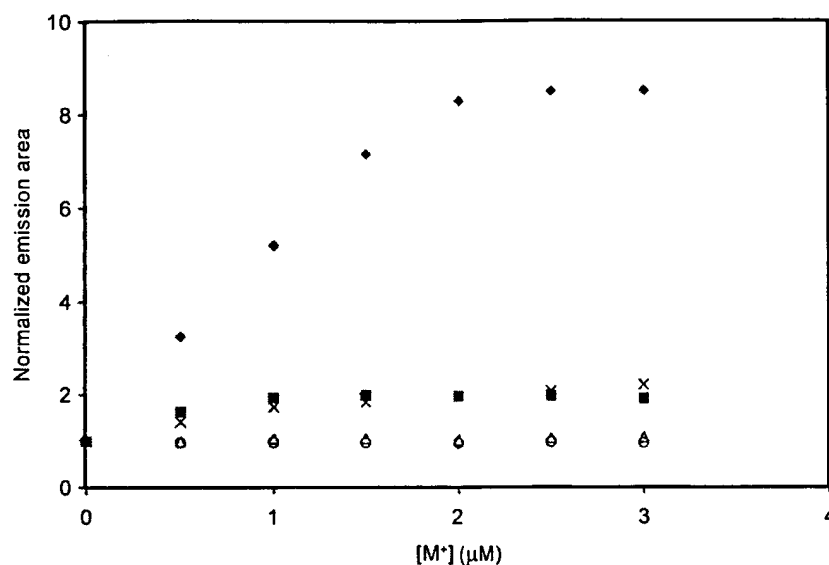


Fig. 3. Emission area of II versus the concentration of various alkali metal ions: Li (○), Na (Δ), K (◆), Rb (■), Cs (×).

As shown above, the main advantage of the compound of the Benco reference is that the compound binds to potassium and not to lithium. Combining the Pacey reference, or any reference, with the Benco reference to produce a compound capable of binding to lithium would render the prior art invention being modified unsatisfactory for its intended purpose.

Finally, the Office Action cites the Barnard reference to cure the deficiencies of the Benco reference and the Pacey reference. The Office Action states:

In the patent and published application Barnard teaches covalently immobilized fluoroionophores as **optical metal ion sensors...** Fluoroionophores that are fictionalized with reactive groups may be covalently bound to inorganic or organic carrier materials and are used as active components in polymer membranes of optical sensors for the detection of ions. The sensors are distinguished by a long usable life and a high degree of sensitivity. **In the formula taught, and ionophore, I, can have a number of forms and are natural or synthetic organic compounds that contain a plurality of mostly alternating electron-rich hetero atoms such as, for example, S, N and especially O, in an open-chained or cyclic carbon chain and that enable the ions to be measured to be selectively complexed.** Column 2, line 60 to column 3, line 7 teach these ionophores derived from substances that have an oligoether, polyether, oligoester, polyester, oligoamide or polyamide structure. **Examples of such suitable substances may be crown ethers, coronandenes, cryptandenes, calixarenes, podandene or derivatives thereof, also cyclic peptides, for example valinomycin, nonactin,**

**peptides such as gramicidin, and peptides which in the presence of the ion to be determined change their secondary, tertiary or quaternary structure for bonding the ion;** it is also possible to use tetrahydrofuran-containing macrolides bonded via ester bridges, and analogous substances that are able to regulate transport in biological systems, or cyclic oligosaccharides, such as, for example, cyclodextrins or cyclophanes...(August 18, 2004 Office Action; Pages 3-4)(Emphasis added).

As such, the Barnard reference teaches binding a wide variety of compound to a sensor so that these compounds can detect various concentrations. However, the Barnard reference does NOT disclose how one would modify the calixarene of the Benco reference so that the compound would no longer selectively bind potassium ions and would now selectively bind potassium ions. In disclosing cations that may be detected with the disclosed monitor, the Barnard reference discloses:

Cations are, for example, cations of metals from main groups I to V and sub-groups I to VIII of the Periodic Table of the Elements, the lanthanides and actinides. Examples of metals include Li, Na, K, Rb, Cs, Mg, Ca, Sr, Ba, B, Al, Ga, In, Tl, Sn, Pb, Sb, Bi, Cu, Ag, Au, Zn, Cd, Hg, Sc, Y, Ti, Zr, Hf, Cr, Mo, W, Mn, Fe, Co, Ni, Ru, Os, Rh, Ir, Pt, Pd, La, Ce, Pr, Nd, Pm, Sm, Eu, Gd, Tb, Dy, Ho, Er, Yb, Lu, Ac, Th, Pa, U, Np, Pu. **Preferred cations are the alkali metal and alkaline earth metal ions, especially  $\text{Li}^+$ ,  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Mg}^{2+}$ ,  $\text{Ca}^{2+}$  and  $\text{Sr}^{2+}$ , and more especially  $\text{K}^+$ ,  $\text{Na}^+$  and  $\text{Ca}^{2+}$ .** Suitable ammonium cations are, for example,  $\text{NH}_4^+$  and the cations of protonated primary, secondary and tertiary amines and of quaternary ammonium. The amines may contain from 1 to 40, especially from 1 to 20 and more especially from 1 to 12, carbon atoms. The quaternary ammonium may contain from 4 to 40, especially from 4 to 20, and more especially from 4 to 16, carbon atoms. **Furthermore, organic ions, for example oligoalkylammonium ions, phosphonium ions, guanidine ions or choline ions, may be selectively bonded.**

The Barnard reference discloses that the disclosed compound may be used with " **$\text{Li}^+$ ,  $\text{Na}^+$ ,  $\text{K}^+$ , ...**" but the disclosure gives no indication that the Barnard compound can selectively bind any of these ions. The Barnard reference points out that "**[f]urthermore, organic ions, for example oligoalkylammonium ions, phosphonium ions, guanidine ions or choline ions, may be selectively bonded.**" As such, it appears that the remaining ions in the list--including  $\text{Li}^+$ ,  $\text{Na}^+$ ,  $\text{K}^+$  may NOT be selectively bonded. Even if the argument could be made that Barnard teaches a compound that can selectively bind Li, K and Na ions, the reference certainly does not teach,

disclose or suggest how to modify the calixarene of the Benco reference so that the compound will no longer selectively bind potassium ions and will now selectively bind lithium ions.

In conclusion, Applicants respectfully contend that there is no motivation to combine the references of Benco, Pacey and Barnard. Further, the primary purpose of the Benco reference is to disclose a calixarene capable of binding potassium and not binding to lithium. As such, there is no motivation to modify the calixarene of the Benco reference to create a calixarene that would bind lithium ions and not bind potassium ions--such a modification would **render the Benco calixarene being modified unsatisfactory for its intended purpose**. Therefore, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. §103(a) and request reconsideration and allowance of pending claims 1-53.

**Claims Rejected Under Obviousness-Type Double Patenting:**

The Office Action rejected claims 1-53 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-28 of U.S. Patent No. 6,660,526 to Benco et al. ("the '526 patent") in view of the Benco, Pacey and Barnard references. The Office Action stated:

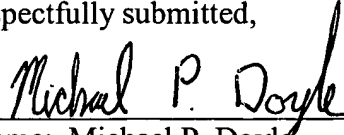
The patented claims are directed to a molecule, device and method that encompass the molecule, device and method taught by Benco above, therefore they differ from the instant claims as the Benco reference differs from the instant claims. **Thus for the reasons given above, the instant claims are obvious in view of the patented claims.** (August 18, 2004 Office Action, Page 5)(Emphasis added).

As noted by the Office Action, the Benco reference (discussed above) discloses the same subject matter as the '526 patent--that is, both disclose a calixarene which selectively binds to potassium ions and does NOT bind to lithium ions. For the same arguments discussed above, Applicants respectfully requests withdrawal of the rejection under the judicially created doctrine of obviousness-type double patenting and allowance of pending claims 1-53.

Applicants submit that all claims are allowable as written and respectfully request early favorable action by the Examiner. If the Examiner believes that a telephone conversation with Applicants' attorney would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney of record.

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Respectfully submitted,

A handwritten signature in black ink, reading "Michael P. Doyle", written over a horizontal line.

Name: Michael P. Doyle

Registration No.: 49,052

Customer No.: 29932

Palmer & Dodge LLP

111 Huntington Avenue

Boston, MA 02199-7613

Tel. (617) 239-0100